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Altered heart rate variability and ventricular repolarization in children with mitral valve prolapse

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ABSTRACT

Objective: The aim of this study was to evaluate heart rate variability (HRV) parameters and ventricular repolarization abnormalities in children with mitral valve prolapse (MVP) compared with healthy controls.

Materials and Methods: This retrospective single-center study included 78 children with MVP and 92 healthy controls with similar age and gender distributions. Demographic characteristics, 24-hour Holter-derived HRV parameters, and electrocardiographic measurements were analyzed. HRV indices included SDNN, SDANN, SDANNi, rMSSD, pNN50, total power, VLF, LF, HF, LF/HF ratio, and triangular index. Multiple comparisons were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method. Multivariable linear regression analyses adjusted for age and sex were performed for selected representative variables.

Results: Children with MVP demonstrated significantly lower SDANNi, rMSSD, total power, LF, HF, and triangular index values compared with controls after FDR correction. Maximum QTc values were significantly higher in the MVP group. In multivariable regression analysis, MVP remained independently associated with lower HF and rMSSD values and higher maximum QTc values after adjustment for age and gender. No significant differences were observed for LF/HF ratio, SDNN, SDANN, or pNN50 after FDR correction.

Conclusion: Children with MVP exhibit reduced parasympathetic modulation together with prolonged ventricular repolarization independently of age and gender. These findings suggest that pediatric MVP may be associated with autonomic and electrophysiological alterations.

Keywords: Autonomic nervous system, child, electrocardiography, heart rate, mitral valve prolapse

Introduction

Mitral valve prolapse (MVP) is characterized by the displacement of one or both mitral valve leaflets above the atrioventricular junction during ventricular systole (1). It is often asymptomatic but may present with a wide spectrum of symptoms, including atypical chest pain, palpitations, dyspnea, presyncope, reduced exercise tolerance, migraine-like headaches, anxiety, and depression (2).

Overall, MVP is generally associated with a favorable prognosis; however, complications such as ventricular arrhythmias and sudden cardiac death have been reported in a subset of patients (3,4).

Several studies have investigated autonomic function in patients with MVP using heart rate variability (HRV) analysis, yielding inconsistent results. While some reports have demonstrated reduced parasympathetic activity and impaired autonomic regulation, others have reported no significant differences, and the underlying mechanisms remain incompletely understood (5,6).

Given the potential link between autonomic dysfunction and arrhythmic risk in MVP, further evaluation of HRV parameters may provide valuable insights into the pathophysiology of this condition. Therefore, in this study, we aimed to assess HRV parameters in patients with MVP and compare them with those of healthy controls in order to better characterize autonomic function in this population.

Materials and Methods

This retrospective study was conducted in the pediatric cardiology outpatient clinic of Ankara Bilkent City Hospital as requested and included 78 pediatric patients diagnosed with MVP between January 2022 and September 2025. A total of 92 healthy children with normal echocardiographic findings and similar age distribution were included as the control group.

Inclusion criteria were adequate echocardiographic imaging, displacement of the anterior and/or posterior mitral valve leaflets more than 2 mm beyond the mitral annulus during systole, structurally normal hearts without congenital heart disease, and no use of antiarrhythmic medications. Patients with MVP secondary to conditions such as Marfan syndrome, rheumatic heart disease, Ehlers–Danlos syndrome were excluded from the study.

Twenty-four-hour Holter monitoring recordings were analyzed in all participants. The evaluated HRV parameters included time-domain indices such as SDNN, SDANN, SDANNi, rMSSD, pNN50, triangular index, minimum heart rate, maximum heart rate, and average heart rate, as well as frequency-domain parameters including total power, very low frequency (VLF), low frequency (LF), high frequency (HF), and LF/HF ratio. Maximum corrected QT interval (QTc) values were obtained from 24-hour Holter recordings using CardioScan 12 Holter analysis software (DM Software, USA). QTc values were automatically calculated using Bazett's correction formula, and the maximum QTc value recorded during the monitoring period was used for statistical analysis.

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Normality of distribution was assessed using the Shapiro–Wilk test. Continuous variables were expressed as median (interquartile range) and compared using the Mann–Whitney U test. Categorical variables were presented as frequency and percentages and subsequently subjected to comparison through the utilisation of the Pearson chi-square test. To account for multiple comparisons, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method, which was preferred over more conservative methods because HRV parameters are physiologically interrelated. In addition, multivariable linear regression analyses adjusted for age and gender were performed for selected representative variables. A p-value <0.050 was considered statistically significant.

Results

A total of 170 children were included in the study, consisting of 78 patients with MVP and 92 healthy controls. The median age was 9.5 years in the MVP group and 10.1 years in the control group, with no significant difference between the groups (p=0.536). Female gender was present in 88.5% of the MVP group and 84.7% of the control group, with no significant difference between the groups (p=0.905).

Comparisons of HRV parameters between the groups are presented in Table I. Patients with MVP demonstrated significantly lower SDANNi, rMSSD, total power, LF, HF, and triangular index values after FDR correction. In addition, maximum QTc values were significantly higher in the MVP group. No significant differences remained after FDR correction for SDNN, SDANN, pNN50, VLF, LF/HF ratio, minimum heart rate, maximum heart rate, or average heart rate.

Given the interrelated nature of HRV parameters, representative variables reflecting parasympathetic modulation and ventricular repolarization were selected for multivariable regression analysis. MVP remained independently associated with lower HF and rMSSD values after adjustment for age and gender (p=0.001 and p=0.012, respectively). Maximum QTc also remained significantly associated with MVP after adjustment (p=0.026). In addition, age and gender were independent predictors of QTc (Table II).

Table I: Comparison of HRV parameters between MVP and control groups

	MVP	Control	p	p (FDR)
Age*	9.5 (6.4)	10.1 (4.2)	0.536	0.573
Female†	69 (88.5)	78 (84.7)	0.905	-
SDNN*	121 (53)	137 (45)	0.075	0.086
SDANN	110 (47)	120 (45)	0.215	0.246
SDANNi*	58 (26)	66 (18)	0.009	0.029
rMSSD*	38 (14)	48 (19)	0.015	0.034
pNN50*	15 (10)	18 (13)	0.044	0.078
Total Power*	2964 (2902)	4298 (2123)	0.005	0.020
VLF*	1735 (1646)	2543 (1207)	0.072	0.086
LF*	711 (541)	974 (400)	0.005	0.020
HF*	452 (318)	607 (444)	0.002	0.016
LF/HF*	1.49 (0.94)	1.65 (0.77)	0.388	0.414
Triangular index*	31.8 (10.6)	34.7 (11.9)	0.011	0.029
Max QTc*	469 (60)	415 (75)	<0.001	0.008
Min HR*	51 (8)	51 (7)	0.624	0.624
Max HR*	154.5 (17)	161 (26)	0.229	0.262
average HR*	86 (13)	84 (7)	0.037	0.074

:** *median (IQR) (Mann–Whitney U test),* **†:** *n(%) (Pearson chi-square test),* ***HRV: *heart rate variability,* ***MVP:*** *Mitral valve prolapse,* ***QTc:*** *corrected QT interval,* ***HR:*** *heart rate.* ***p (FDR):*** *p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method.*

Discussion

In the present study, children with MVP demonstrated significant alterations in HRV parameters together with prolonged maximum QTc values compared with healthy controls. The main finding of our study is that pediatric MVP patients exhibit impaired autonomic modulation, particularly reduced parasympathetic (vagal) activity. Given the interrelated nature of HRV parameters, representative variables reflecting parasympathetic modulation and ventricular repolarization were selected for multivariable regression analysis. In this analysis, MVP remained independently associated with lower HF and rMSSD values as well as higher maximum QTc values after adjustment for age and gender.

Our analysis demonstrated that patients with MVP had significantly lower SDANNi, rMSSD, total power, LF, HF, and triangular index values compared with healthy controls. Among these, HF and rMSSD are considered reliable indicators of parasympathetic modulation and reflect short-term beat-to-beat variability (7,8). Interestingly, SDANNi was significantly reduced whereas SDANN remained unchanged. Since SDANNi reflects short-term fluctuations in autonomic modulation, this finding may suggest that autonomic impairment in MVP predominantly affects short-term HRV dynamics rather than longer-term variability (7,9). The independent association of HF and rMSSD, two established markers of parasympathetic modulation, with MVP in our

Table II: Multivariable linear regression analyses adjusted for age and gender

Predictor	B	SE B	β	t	p	95% CI for B	R^2
HF							
Gender	226.783	76.160	0.221	2.978	0.003	76.415-377.151	0.121
Age	1.958	8.229	0.017	0.238	0.812	-14.288-18.205	
MVP vs. control	187.098	57.061	0.241	3.279	0.001	74.439-299.758	
rMSSD							
Gender	16.161	3.874	0.305	4.171	<0.001	8.512–23.809	0.144
Age	-0.115	0.419	-0.020	-0.274	0.784	-0.94-0.712	
MVP vs. control	7.353	2.903	0.184	2.533	0.012	1.622-13.083	
Maximum QTc							
Gender	-53.850	11.536	-0.342	-4.668	<0.001	-76.634-31.066	0.186
Age	-3.383	1.239	-0.198	-2.730	0.007	-5.831-0.936	
MVP vs. control	-19.813	8.786	-0.164	-2.255	0.026	-37.165-2.460	

***HF:** high frequency, **MVP:** mitral valve prolapse, **rMSSD:** root mean square of successive differences, **QTc:** corrected QT interval, **B:** unstandardized regression coefficient, **SE:** standard error, **β:** standardized regression coefficient, **CI:** confidence interval, **R^2:** coefficient of determination*

regression analysis supports the presence of reduced vagal activity in these patients (10,11). These findings are consistent with the study by Han et al. (12), which reported significantly lower time-domain and frequency-domain HRV indices, including HF, LF, and rMSSD, in children with MVP.

Similarly, Ahmadi et al. (6) demonstrated a decline in several HRV parameters, including SDNN, SDANN, rMSSD, and pNN50, in children with MVP, suggesting autonomic dysfunction in these patients. In contrast, Beyazal et al. (13) did not find significant differences in overall time- and frequency-domain HRV parameters between MVP patients and controls, reporting only a lower minimum heart rate and a higher prevalence of low LF values in the MVP group. The relatively large sample size of our study, together with the use of FDR correction and multivariable regression analysis, strengthens the evidence supporting impaired parasympathetic modulation in pediatric MVP.

Previous studies evaluating ventricular repolarization in MVP have reported heterogeneous findings. While several studies demonstrated prolonged QTc intervals and increased QT dispersion in pediatric MVP patients, others failed to detect significant QTc prolongation compared with healthy controls (6,13-15). In our cohort, maximum QTc values were significantly higher in the MVP group and remained independently associated with MVP after adjustment for age and gender. The QT interval and its corrected value (QTc) reflect ventricular depolarization and repolarization, and QTc prolongation is a recognized marker associated with an increased risk of ventricular arrhythmias (16,17). Taken together, our findings suggest that autonomic dysregulation and ventricular repolarization abnormalities may coexist in children with MVP.

Our multivariable regression analysis identified age and gender as independent predictors of QTc. Physiological maturation and gender-related differences are known to influence autonomic tone, HRV parameters, and ventricular repolarization in children (18,19). Therefore, adjustment for these variables is important when evaluating autonomic function and repolarization abnormalities in pediatric MVP populations.

Interestingly, although some previous studies reported increased LF/HF ratios in MVP patients, suggesting altered sympathovagal balance, other studies failed to demonstrate significant differences in HRV parameters between MVP patients and controls (12,20,21). In our cohort, LF/HF ratio was not significantly different after FDR correction. Similarly, SDNN, SDANN, and pNN50 values were not significantly different between groups. These findings may suggest that autonomic alterations in our pediatric MVP cohort are more closely related to reduced parasympathetic modulation rather than sympathetic predominance.

Limitations

Our study has several limitations. First, the retrospective design limits the ability to establish causal relationships between the observed autonomic and repolarization abnormalities and future clinical outcomes. In addition, long-term prospective follow-up studies are needed to determine whether reduced HRV parameters and prolonged QTc values in pediatric MVP patients are associated with clinically significant arrhythmic events or syncope later in life.

Conclusion

In conclusion, children with MVP demonstrated altered parasympathetic modulation and prolonged ventricular repolarization independently of age and gender. These findings suggest that pediatric MVP may be associated with autonomic and electrophysiological alterations, highlighting the potential importance of cardiac autonomic assessment and electrocardiographic evaluation in this population. Although these findings do not warrant changes in current clinical management, they may provide additional information in the clinical evaluation of children with MVP. Whether these abnormalities predict future arrhythmic events and should influence follow-up strategies remains to be determined.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (01.10.2025, reference number: TABED 2-25-1546).

Contribution of the authors

UP: conceived and designed the study, collected the data, and drafted the initial manuscript, İİÇ: critically reviewed the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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Conflict of interest
The authors declare that there is no conflict of interest.

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